

## REMARKS

The Examiner rejected claim 25 as allegedly not complying with 35 U.S.C. 112, first paragraph, written description requirement.

Although Applicants disagree, to expedite prosecution, Applicants have cancelled claim 25 without prejudice. Accordingly, the rejection has been rendered moot.

The Examiner rejected claims 9 and 12-25 under 35 U.S.C. 103(a) as allegedly being unpatentable over Asano, in view of Finkenaur. The Examiner alleges that the Declaration is not persuasive. Specifically, the Examiner alleges that because “solubility, and thus the stabilization properties of the polysaccharide are dependent upon not only the type of polysaccharide used but also for example upon the degree of substitution of the polysaccharide”, “one of ordinary skill in the art would have found it obvious to provide the desired polysaccharides, and to optimize and/or adjust the degree of substitution of the polysaccharides.” (Par. bridging pages 11 and 12 of the Office Action dated March 5, 2008). The Examiner further contends that “properties such as the length of the polysaccharide can affect the solubility and thus the stabilization properties of the polysaccharide. Accordingly, the Examiner contended that it is not considered unexpected that using hydroxypropyl cellulose results in a remaining ratio of bFGF after 7 days of 94.9%, whereas compositions using methyl cellulose or hydroxypropyl methyl cellulose only result in a less than 88% remaining ratio of bFGF (Page 10 of the Office Action dated March 5, 2008).

Applicants respectfully disagree. The generalized statements provided by the Examiner are not sufficient to ignore actual evidentiary facts with respect to the particular combination used in the presently claimed method.

The two Ohkuma Declarations submitted to the attention of the Examiner set forth specific facts showing why a skilled artisan would not have known or expected that using the specific combination of bFGF provides unexpected results. The Examiner completely ignores the fact that Finkenaur specifically equates **all** the named different stabilizers as equally “preferred.” Thus, all a skilled artisan could and would infer based on Finkenaur was that **all these agents result in equally good combination**. Only the present application teaches that a significantly better result can be achieved using the specific combination.

The discussion of solubility only dealt with compositions in general. Finkenaur, then taking all of this into account, taught that certain compounds were equally preferred. Not that

hydroxypropyl cellulose was better than, for example – methyl cellulose or hydroxypropyl methyl cellulose.

The two Ohkuma Declarations have provided facts with respect to specific properties of different stabilizers in combination with bFGF. The results show one of the several different polysaccharides that were disclosed in Finkenaur worked unexpectedly better than all the others in the methods of the present invention. For example, at page 6 of the Declaration signed on October 31, 2007, Dr. Ohkuma stated that “cellulose **derivative other than hydroxypropyl cellulose** of the present invention **cannot be practically used**” (emphasis added). This is because, as explained by Dr. Ohkuma “a standard range of a medicament is generally determined in the range of “95-105%”, so that if the remaining ratio of bFGF is 88% or less, it is far from the standard content.” (Id.)

The difference between having a pharmaceutically effective amount of bFGF at opposed to a lower amount establishes the unexpected superiority of the results.

Moreover, Applicants also submit that the Examiner’s reliance on Finkenaur is misplaced. The prior art teaches that stabilization for EGF and bFGF is not similar. For example, EGF is relatively stable under conditions where bFGF is not. All the examples of Finkenaur concern EGF, not bFGF. However, Caldwell et al. (attached herewith as Exhibit A), describe that bFGF and EGF had different stabilities and responded differently to a different stabilizing agent, namely, heparin. Thus, not only does Finkenaur NOT disclose the superiority of the combination of bFGF with hydroxypropyl ether derivative of cellulose, containing 53.4-77.5% of hydroxypropyl group when a dried material is determined, Finkenaur also does not show that a bFGF would work with any of the disclosed stabilizers. Therefore, in attempting to stabilize bFGF, a skilled artisan would have not necessarily expected the same agents to work that worked for EGF.

Applicants also submit, that Finkenauer’s teachings are general with respect to use of a range of different polysaccharide stabilizers in combination with a range of different polypeptide growth factors. The specific bFGF hydroxypropyl ether derivative of cellulose combination needed for the methods of the present invention is not described. Importantly, as can be seen from Dr. Ohkuma’s Declaration (page 6 of the Declaration signed on October 31, 2007), the method of the present invention needs high stability combination for it to work. There is nothing

in Finkenaur or Asano that would guide a skilled artisan to the specific combination. Moreover, even if the specific combination had been shown to work particularly well with EGF, a skilled artisan would not have necessarily expected it to work equally well with bFGF, as evidenced by Caldwell et al.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Applicants herewith authorize the Commissioner to charge any fee deficiencies and credit any overpayments to Nixon Peabody LLP Deposit Account No. 50-0850.

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Respectfully submitted,

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